Clinical potential of aclidinium bromide in chronic obstructive pulmonary disease

Paul W Jones
Institute for Infection and Immunity,
Faculty of Respiratory Medicine,
St George’s, University of London,
London, UK

Abstract: Three long-acting muscarinic antagonists (LAMAs) are now available in Europe, providing clinicians and patients with a choice of interventions, which is important in COPD, which is clinically a heterogeneous disease. The first LAMA, tiotropium, has been widely used over the last decade as a once-daily maintenance therapy in stable COPD to improve patients’ health-related quality of life and to reduce the risk of exacerbations. Administered via the HandiHaler® device, it is safe and well tolerated. Another new once-daily LAMA, glycopyrronium, has also been shown to improve health status and reduce exacerbations, and is well tolerated. The subject of this review is a third LAMA, aclidinium bromide, which was approved as a twice-daily maintenance bronchodilator treatment. In the pivotal Phase III clinical trials, patients receiving aclidinium achieved significantly greater improvements in lung function, reductions in breathlessness, and improvements in health status compared with placebo, for up to 24 weeks. In continuation studies, these improvements were sustained for up to 52 weeks. Pooled data showed exacerbation frequency was significantly reduced with aclidinium versus placebo. Preclinical and pharmacological studies demonstrating low systemic bioavailability and a low propensity to induce cardiac arrhythmias were translated into a favorable tolerability profile in the clinical trial program – the adverse event profile of aclidinium was similar to placebo, with a low incidence of anticholinergic and cardiac adverse events. While additional studies are needed to evaluate its full clinical potential, aclidinium is an important part of this recent expansion of LAMA therapeutic options, providing clinicians and patients with an effective and well-tolerated COPD treatment.

Keywords: aclidinium bromide, anticholinergic, long-acting muscarinic antagonist, chronic obstructive pulmonary disease, multidose dry powder inhaler

Introduction

Anticholinergic agents play a key role in COPD management, being recommended as a first choice, either as monotherapy or in combination with a long-acting β2-agonist (LABA).1 For around a decade, only one long-acting muscarinic agonist (LAMA) – tiotropium bromide – was available, but this picture changed in 2012, with the approval of two new LAMAs – aclidinium bromide and glycopyrronium bromide. All three LAMAs are noted as potential treatment options in the recent update from the Global Initiative for Chronic Obstructive Lung Disease (GOLD).2

Tiotropium bromide

Tiotropium has been widely used over the last decade as once-daily maintenance therapy in stable COPD. Currently, it can be delivered via the HandiHaler®, a single-dose dry powder inhaler, and the Respinmat®, a soft mist device which is a propellant-free, multidose inhaler. It has been extensively studied in patients with COPD – a recent Cochrane review identified 22 studies of good methodological quality that had enrolled...
23,309 participants with COPD. This review showed that tiotropium improved patients’ health-related quality of life and reduced exacerbations and hospitalization.

In the 4-year Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial using tiotropium via the HandiHaler® in moderate to severe COPD, improvements in forced expiratory volume in 1 second (FEV₁) compared with placebo were maintained throughout the trial (ranging from 87 to 103 mL pre-bronchodilator). The mean number of exacerbations was reduced by 14% and mean total St George’s Respiratory Questionnaire (SGRQ) score was higher than with placebo at each time point throughout the 4-year period by 2.3 to 3.3 units. However, the rate of decline in FEV₁ – the primary outcome of the trial – was not significantly reduced by the use of tiotropium.

In the UPLIFT trial, overall rates of serious cardiac adverse events (AEs) were all significantly lower in the tiotropium group than the placebo group (relative risk [RR]=0.84), although mortality was not significantly lower. Other publications have described conflicting observations regarding tiotropium and cardiovascular risk, including a new user cohort study in the UK, which identified a numerically (but not significantly) increased risk of stroke with tiotropium HandiHaler® versus LABA, but a significantly lower all-cause mortality (hazard ratio [HR]=0.70). In recent years, there has been increasing concern that tiotropium delivered via the Respimat® may have been associated with higher mortality, but the large, randomized Tiotropium Safety and Performance in Respimat® study (TioSPIR; NCT01126437), in which outcomes with tiotropium via Respimat® (2.5 and 5 µg doses) and HandiHaler® (18 µg) were compared in over 17,000 patients, showed no difference in all-cause mortality and no difference in efficacy as measured by exacerbation rate.

**Glycopyrronium bromide**

Glycopyrronium bromide is a synthetic quaternary ammonium compound, which has been used for many years to reduce secretions and block cardiac vagal reflexes before surgery. Previously it was administered orally or as an injection, but a dry-powder formulation has now been developed, administered once daily (QD) via a single dose dry-powder device – the Breezhaler®. Following promising results in early preclinical and clinical studies, a Phase III development program called GLycopyrronium bromide in COPD airWays (GLOW) was developed and has shown that glycopyrronium 50 µg QD improved trough FEV₁, breathlessness, and health status, and reduced exacerbations.

In the GLOW 3 trial, glycopyrronium treatment was superior to placebo with respect to exercise endurance time after 3 weeks of treatment. The program also showed that it had an acceptable safety profile and low incidence of cardiac and anticholinergic AEs.

**Aclidinium bromide**

Aclidinium bromide 400 µg has been approved for the maintenance treatment of COPD. It has a twice-daily (BID) dosing regimen and is delivered by a multidose dry powder device named Genuair® in the EU and Pressair® in the USA.

**Pharmacologic and pharmacokinetic profile**

Preclinical studies have shown that aclidinium displays high affinity for all five muscarinic receptors, with kinetic selectivity for M₁ receptors over M₂, and a shorter duration of action and a faster onset compared with tiotropium bromide. The drug’s preclinical cardiac safety profile is also favorable.

Pharmacokinetic studies in healthy volunteers showed that it is poorly absorbed into plasma and rapidly hydrolyzed into two major inactive metabolites, resulting in limited systemic exposure. Further studies in healthy individuals demonstrated that steady state was achieved within 2 days for aclidinium at all doses tested and that there was no effect on the QT interval at doses of up to 800 µg BID. Renal impairment does not appear to increase systemic exposure to aclidinium, and its pharmacokinetic profile appears to be similar in younger (40–59 years of age) and more elderly (≥70 years of age) patients with COPD.

**Efficacy and safety**

Aclidinium has been extensively evaluated in patients with COPD (Table 1) and has also been the subject of a recent Cochrane systematic review. Early studies of aclidinium examined a QD schedule, but while in a dose of 200 µg QD it significantly improved trough FEV₁ in patients with COPD versus placebo, the improvement (59–67 mL) was below the suggested minimum clinically important difference (MCID) of 100 mL, although significant improvements in breathlessness and health status were seen and exacerbations were reduced.

Subsequently, studies investigating higher doses and alternative dosing regimens were conducted leading to two Phase III studies: the 12-week AClidinium in Chronic Obstructive Respiratory Disease I (ACCORD COPD I) study (Figure 1A) and the 24-week Aclidinium To Treat Airway obstruction In COPD PatieNts (ATTAIN) study (Figure 1B).
### Table 1 Overview of Phase II, Phase III, and long-term trials of aclidinium in COPD

<table>
<thead>
<tr>
<th>Study acronym and reference</th>
<th>Study treatments</th>
<th>N</th>
<th>Duration (weeks)</th>
<th>Key efficacy results treated vs placebo, respectively; impact on trough and peak FEV₁</th>
<th>Key safety results: most common AEs (&gt;10% patients in any group); cardiac AEs, anticholinergic AEs</th>
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<tbody>
<tr>
<td><strong>BID dosing studies</strong></td>
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</tbody>
</table>
| Phase II Fuhr et al[9] | Aclidinium 400 µg BID Placebo Tiotropium 18 µg QD | 30 | 2 | Change from baseline in FEV₁, AUC₁₈–₀₂, at Day 15 vs placebo  
• Aclidinium 400 µg: 221 mL (P<0.0001)  
• Tiotropium 18 µg: 244 mL (P<0.0001) | | |
| NCT00868231 | | | | | |
| Phase II Singh et al[10] | Aclidinium 100, 200, 400 µg BID Placebo Formoterol 12 µg BID | 79 | 1 | Change from baseline in FEV₁, AUC₁₈–₀₂, at Day 7 vs placebo  
• Aclidinium 100 µg: 154 mL (P<0.0001)  
• Aclidinium 200 µg: 176 mL (P<0.0001)  
• Aclidinium 400 µg: 208 mL (P<0.0001)  
• Formoterol 12 µg: 210 mL (P<0.0001) | | |
| NCT01120093 | | | | | |
| ACCORD COPD I (Phase III) Kerwin et al[11] | Aclidinium 200 µg BID Placebo | 185 | 12 | Trough FEV₁ change from baseline vs placebo  
• Aclidinium 200 µg: 86 mL (95% CI 45–127; P<0.0001)  
• 400 µg: 124 mL (95% CI 83–164; P<0.0001) | | |
| NCT00891462 | | | | | |
| ATTAIN (Phase III) Jones et al[12] | Aclidinium 200 µg BID Placebo | 277 | 24 | Trough FEV₁ change from baseline vs placebo  
• Aclidinium 200 µg: 99 mL (P<0.0001)  
• 400 µg: 128 mL (P<0.0001) | | |
| NCT01001494 | | | | | |
| ACCORD COPD II (Phase III) Rennard et al[13] | Aclidinium 200 µg BID Placebo | 182 | 12 | Trough FEV₁ change from baseline vs placebo  
• Aclidinium 200 µg: 185 mL (P<0.0001)  
• 400 µg: 209 mL (P<0.0001) | | |
| NCT01045161 | | | | | |
| ACCORD COPD I extension D'Urzo et al[14] | Aclidinium 200 µg BID Placebo (patients previously receiving placebo re-randomized to one of the two aclidinium doses) | 291 | 52 | Improvements in peak and trough FEV₁ achieved during the lead-in phase were maintained to the end of the extension phase (Week 64)  
Improvements from baseline in trough FEV₁ in patients receiving aclidinium throughout  
• 200 µg: 62–127 mL  
• 400 µg: 56–140 mL  
Improvements from baseline in peak FEV₁ in patients receiving aclidinium throughout  
• 200 µg: 213 mL  
• 400 µg: 219 mL | | |
| NCT00970268 | | | | | |

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Adverse events reported by seven patients receiving aclidinium, eight receiving placebo, and three receiving tiotropium  
Most common AE was COPD exacerbation (three patients all receiving placebo)  
The safety profile of aclidinium was comparable to placebo  
Aclidinium 200 µg: no event >10% (COPD exacerbation, 9.2%); <2% cardiac and anticholinergic AEs  
Aclidinium 400 µg: no event >10% (COPD exacerbation, 7.4%); <2% cardiac and anticholinergic AEs  
Placebo: COPD exacerbation (12.4%); <2% cardiac and anticholinergic AEs  
Aclidinium 200 µg: COPD exacerbation (15.9%), headache (10.8%), nasopharyngitis (11.6%); <1% cardiac and anticholinergic AEs  
Aclidinium 400 µg: COPD exacerbation (14.1%), headache (12.3%), nasopharyngitis (11.2%); <2% cardiac and <1% anticholinergic AEs  
Placebo: COPD exacerbation (20.5%), headache (8.1%), nasopharyngitis (8.4%); <2% cardiac and anticholinergic AEs  
Aclidinium 200 µg and 400 µg had a similar AE profile to placebo, with a similar number of patients in each group experiencing a severe AE or an AE leading to discontinuation.  
Exacerbation of COPD was the only AE reported in more than 5% of patients in any treatment group, occurring in 11.5% of placebo group, 8.7% of aclidinium 200 µg group, and 13.0% of aclidinium 400 µg group  
<2% cardiac AEs; <2% anticholinergic AEs  
Aclidinium 200 µg: COPD exacerbation (25.5%); <2% cardiac and <3.5% anticholinergic AEs  
Aclidinium 400 µg: COPD exacerbation (21.7%); <2% cardiac and <3.5% anticholinergic AEs
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Study acronym and reference</th>
<th>Study treatments</th>
<th>N</th>
<th>Duration (weeks)</th>
<th>Key efficacy results treated vs placebo, respectively: impact on trough and peak FEV₁</th>
<th>Key safety results: most common AEs (&gt;10% patients in any group); cardiac AEs, anticholinergic AEs</th>
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<tbody>
<tr>
<td>LAS-MD-35 (Phase III)</td>
<td>Aclidinium 200 µg BID</td>
<td>312</td>
<td>52</td>
<td>Trough FEV₁ change from baseline at Week 52 (maximal values during the study):</td>
<td>Aclidinium 200 µg COPD exacerbation (19.3%); &lt;2% cardiac and &lt;3.5% anticholinergic AEs</td>
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<td>Aclidinium 400 µg BID</td>
<td>293</td>
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<td>• 200 µg: 34 mL (62 mL)</td>
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<td>• 400 µg: 72 mL (101 mL)</td>
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<td>Peak FEV₁ change from baseline at Week 52 (maximal values during the study):</td>
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<td>• 200 µg: 185 mL (226 mL)</td>
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<td>• 400 µg: 214 mL (235 mL)</td>
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<tr>
<td>LAS39 (Phase IIIb)</td>
<td>Aclidinium 400 µg BID</td>
<td>171</td>
<td>6</td>
<td>Difference from placebo in change from baseline in FEV₁, AUC₀–₂₄</td>
<td>AE incidence (28.0% overall) was similar between treatment groups, with few patients experiencing anticholinergic AEs (&lt;1.5%, any group)</td>
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<td>• Aclidinium 200 µg BID: 150 mL (P&lt;0.0001)</td>
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<td></td>
<td>Tiotropium 18 µg QD</td>
<td>158</td>
<td></td>
<td>• Aclidinium 18 µg QD: 140 mL (P&lt;0.0001)</td>
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<td></td>
<td>Placebo</td>
<td>85</td>
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<td>Difference from placebo in change from baseline in FEV₁, AUC₁₂–₂₄</td>
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<td>• 400 µg aclidinium BID: 160 mL (P&lt;0.00001)</td>
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<td></td>
<td>• 18 µg tiotropium QD: 123 mL (P&lt;0.00001)</td>
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<tr>
<td>QD dosing studies</td>
<td></td>
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<td>Aclidinium was well tolerated, with no dose-dependent effect on EKG, laboratory parameters or AEs</td>
</tr>
<tr>
<td>Phase II</td>
<td>Aclidinium 25, 50,100, 200 or 400 µg QD</td>
<td>464</td>
<td>4</td>
<td>Difference from placebo in change from baseline in trough FEV₁, at Day 29</td>
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<tr>
<td></td>
<td>Tiotropium 18 µg QD</td>
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<td></td>
<td>• Aclidinium 200 µg QD: 148 mL (P=0.006)</td>
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<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>• Aclidinium 400 µg QD: 128 mL (P=0.018)</td>
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</tr>
<tr>
<td>Phase II</td>
<td>Aclidinium 100, 300 or 900 µg QD</td>
<td>17</td>
<td>Single doses</td>
<td>Mean area under the FEV₁ curve (0–24h time interval) was 1.58 L for placebo and 1.73 L, 1.79 L, and 1.82 L for 100, 300, and 900 µg aclidinium, respectively (P&lt;0.001 vs placebo for all aclidinium doses)</td>
<td>Well tolerated, no anticholinergic side effects reported, no clinical effect on EKG parameters</td>
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<tr>
<td></td>
<td>Placebo</td>
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<tr>
<td>ACCLAIM COPD I</td>
<td>Aclidinium 200 µg QD</td>
<td>627</td>
<td>52</td>
<td>Week 12 trough FEV₁ change from baseline vs placebo:</td>
<td>Aclidinium 200 µg nasopharyngitis (16.3%); headache (11.3%); cardiac AEs 5.1%; dry mouth 1%</td>
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<tr>
<td>Jones et al</td>
<td>Placebo</td>
<td>216</td>
<td></td>
<td>61 mL (P&lt;0.001)</td>
<td>Placebo: nasopharyngitis (14.4%); headache (12.5%); cardiac AEs 6.5%; dry mouth 0.9%</td>
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<tr>
<td>NCT00363896</td>
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<td>Week 28 trough FEV₁ change from baseline vs placebo:</td>
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<td>67 mL (P&lt;0.001)</td>
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<tr>
<td>ACCLAIM COPD II</td>
<td>Aclidinium 200 µg QD</td>
<td>600</td>
<td>52</td>
<td>Week 12 trough FEV₁ change from baseline vs placebo:</td>
<td>Aclidinium 200 µg nasopharyngitis (12.7%); headache (14.2%); upper respiratory tract infection (10.8%); cardiac AEs 6.8%; dry mouth 0.3%</td>
</tr>
<tr>
<td>Jones et al</td>
<td>Placebo</td>
<td>204</td>
<td></td>
<td>63 mL (P&lt;0.001)</td>
<td>Placebo: nasopharyngitis (11.3%); headache (12.7%); cardiac AEs 8.3%; dry mouth 1.5%</td>
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<td>NCT00358436</td>
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<td>Week 28 trough FEV₁ change from baseline vs placebo:</td>
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<td>69 mL (P&lt;0.001)</td>
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</table>

Abbreviations: ACCLAIM, Aclidinium Clinical trial Assessing efficacy and safety In Moderate to severe COPD patients; ACCORD, Aclidinium in Chronic Obstructive Respiratory Disease I; ATTAIN, Aclidinium To Treat Airway obstruction In COPD PatieNs; AE, adverse event; AUC, area under curve; AUC₁₂–₂₄, area under curve from 0–12hrs; BID, twice daily; CI, confidence interval; EKG, electrocardiogram; FEV₁, forced expiratory volume in 1 second; h, hour; N, number of patients; QD, once daily; vs, versus.
Aclidinium bromide in COPD

These evaluated aclidinium at doses of 200 and 400 µg BID versus placebo. Supportive studies include the 12-week ACCORD COPD II study\textsuperscript{33} and two long-term studies\textsuperscript{34,35} (Table 1). Most recently, a 6-week Phase IIIb trial has compared aclidinium 400 µg BID with placebo and tiotropium QD via the HandiHaler\textsuperscript{36} in patients with stable, moderate to severe COPD.

Impact of aclidinium on lung function

In the ACCORD COPD I study, the mean pre-bronchodilator FEV\textsubscript{1} improved by 124 mL versus placebo (Figure 2A) and peak FEV\textsubscript{1} by 192 mL versus placebo after 12 weeks (Figure 2B). The peak FEV\textsubscript{1} achieved with aclidinium was significantly greater than for placebo from the first dose onwards ($P<0.0001$).\textsuperscript{31} In the 24-week ATTAIN study, the results were very similar: mean improvement in pre-bronchodilator FEV\textsubscript{1} at Week 24 compared with placebo was 128 mL (Figure 3A), and mean improvement in peak FEV\textsubscript{1} at Week 24 was 209 mL. Again, these benefits were seen from the first dose until the end of the study (Figure 3B).\textsuperscript{32} The 12-week ACCORD COPD II study showed smaller improvements in trough FEV\textsubscript{1}, and this result is thought to be due to statistically significant imbalances between study arms in terms of baseline FEV\textsubscript{1} and COPD severity.\textsuperscript{33} Two long-term studies have shown that improvements in FEV\textsubscript{1} from baseline with aclidinium are sustained for up to 52 weeks.\textsuperscript{34,35} The Cochrane meta-analysis confirmed that aclidinium therapy resulted in statistically significant improvements in both trough and peak FEV\textsubscript{1} compared with placebo.\textsuperscript{40}

In a recently reported 6-week trial comparing aclidinium BID with placebo and tiotropium QD in patients with stable, moderate to severe COPD compared with placebo,
improvements in the area under the curve (AUC) over 24 hours were significantly greater with aclidinium (156 mL) than with tiotropium (117 mL, \(P<0.05\)). This difference was largely driven by a significantly greater improvement in overnight AUC with aclidinium (168 mL) compared with tiotropium (100 mL, \(P<0.01\)), most likely arising due to the different pharmacokinetics associated with QD and BID dosing.\(^5\)

Breathlessness, health status, and COPD symptoms with aclidinium

Significant improvements were seen in breathlessness, health status, and COPD symptoms in the pivotal trials. In both ACCORD COPD I and ATTAIN, by the end of the study, compared with placebo, the improvement in transition dyspnea index score reached the MCID.\(^{31,42,43}\) In ATTAIN at Week 24, the improvement over placebo in SGRQ score exceeded the MCID.\(^{42,44}\) In the two 52-week studies, 45% of patients in LAM-35 achieved a clinically significant improvement (\(\geq 4.0\)-unit improvement from baseline) in SGRQ score at Week 52;\(^{43}\) similarly, in the ACCORD COPD I extension at 64 weeks, 64% of patients improved by more than this amount (Figure 4).\(^{35}\)

The clinical study data synthesis presented in the Cochrane review demonstrated significant improvements in transition dyspnea index (eight trials, 4,490 patients) and SGRQ (seven trials, 4,420 patients) with aclidinium therapy compared with placebo. Furthermore, a higher proportion of

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**Figure 2** Change from baseline in (A) trough FEV\textsubscript{1}, and (B) peak FEV\textsubscript{1} at Week 24 in ACCORD COPD I study.

**Notes:** *\(P<0.001\) vs placebo; \(P<0.05, \) \(P<0.01\) vs aclidinium 200 \(\mu\)g. From Kerwin EM, D’Urzo AD, Gelb AF, et al. COPD 2012;9(2):90–101. Copyright © 2012, Informa Healthcare. Reproduced with permission of Informa Healthcare.\(^3\)

**Abbreviations:** ACCORD, ACclidinium in Chronic Obstructive Respiratory Disease I; FEV\textsubscript{1}, forced expiratory volume in 1 second; LS, least squares; SE, standard error.

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**Figure 3** Change from baseline in (A) trough FEV\textsubscript{1}, and (B) peak FEV\textsubscript{1} at Week 24 in ATTAIN study.

**Notes:** Data reported as least squares mean (standard error). \(\# \)\(P<0.0001\) for both treatments vs placebo. There were no statistically significant differences between the two aclidinium arms. Reproduced with permission of the European Respiratory Society: *Eur Respir J*, October 2012 40:830–836; published ahead of print March 22, 2012, doi:10.1183/09031936.00225511.\(^3\)

**Abbreviations:** ATTAIN, Acclidinium To Treat Airway obstruction In COPD patients; BID, twice daily; FEV\textsubscript{1}, forced expiratory volume in 1 second.
patients treated with aclidinium achieved the MCID in each of these measures, compared with placebo.\textsuperscript{40}

In the ACCORD COPD I study,\textsuperscript{11} night-time and morning COPD symptoms were all significantly reduced among patients treated with aclidinium compared with those who received placebo (Figure 5), and the impact of breathlessness on early morning activities was also significantly reduced with aclidinium versus placebo (Figure 6). In the ATTAIN study,\textsuperscript{32} the EXAcerbations of Chronic pulmonary disease Tool-Respiratory Systems (EXACT-RS) daily diary was used as an exploratory outcome measure. This showed that aclidinium improved the total score and the component scores (breathlessness, chest symptoms, and cough and sputum) significantly more than placebo (Figure 7).

**Effect of aclidinium on COPD exacerbations**

The impact of aclidinium BID on COPD exacerbations was examined in pooled analyses of data from ACCORD COPD I and ATTAIN.\textsuperscript{45,46} Two methods were used to capture COPD exacerbations – health care resource utilization, in which an exacerbation was defined as an increase in symptoms on \( \geq 2 \) consecutive days requiring a change in treatment, and EXACT.\textsuperscript{47} Pooled analyses of health care resource utilization assessments showed that aclidinium significantly reduced moderate to severe exacerbation rates by 29% compared with placebo.\textsuperscript{46} The synthesized data in the Cochrane review from ten aclidinium clinical studies in 5,624 patients found that the reduction in moderate exacerbations requiring treatment with systemic steroids...
and/or antibiotics did not reach significance for aclidinium versus placebo, but that aclidinium significantly reduced the frequency of exacerbations requiring hospitalization.\textsuperscript{40} However, it should be noted that these studies were not powered to investigate exacerbations, and the populations included were not enriched by recruiting patients with a history of frequent exacerbations.

Inhaler preference
In two randomized, double-blind, double-dummy, crossover studies (n=109 patients in total), more patients found the Genuair\textsuperscript{®} easier to use than Aerolizer\textsuperscript{®} or HandiHaler\textsuperscript{®} and reported that dose preparation with Genuair\textsuperscript{®} was “very easy” compared with the other two inhalers (65% vs 24% for Genuair\textsuperscript{®} vs Aerolizer\textsuperscript{®}, respectively; 80% vs 53% for Genuair\textsuperscript{®} vs HandiHaler\textsuperscript{®}, respectively).\textsuperscript{48} Overall, more patients expressed a preference for Genuair\textsuperscript{®} compared with Aerolizer\textsuperscript{®} or HandiHaler\textsuperscript{®}.\textsuperscript{48} In a further study, significantly fewer patients made a critical error using Genuair\textsuperscript{®} (10.5%) compared with HandiHaler\textsuperscript{®} (26.7%).\textsuperscript{49}

Safety and tolerability of aclidinium
In the Phase III and IIIb studies, aclidinium exhibited a good tolerability profile (Table 1).\textsuperscript{29–36} In the 12-week ACCORD COPD I study, the overall incidence of AEs was very low and similar in aclidinium- and placebo-treated patients, with no evidence of a dose–harm relationship. In fact, COPD exacerbation was the only AE reported in >5% of patients in any treatment group (placebo, 12.4%; aclidinium 200 \(\mu\)g, 9.2%; aclidinium 400 \(\mu\)g, 7.4%).\textsuperscript{31} Other AEs were headache (\(\leq 3.3\%\)), nasopharyngitis (\(\leq 2.6\%\)), back pain (\(\leq 2.7\%\)), dyspnea (\(\leq 2.6\%\)), and arthralgia (\(\leq 2.6\%\)). A similar picture was observed in the ATTAIN trial, in which the most common AE was...
COPD exacerbation (placebo, 20.5%; aclidinium 200 µg, 15.9%; aclidinium 400 µg, 14.1%), followed by headache (≤12.3%), nasopharyngitis (≤11.6%), back pain (≤4.3%), and rhinitis (≤3.3%). Cardiac AEs and anticholinergic AEs occurred in <2% of patients in any treatment group in the two studies.31,32

The good safety and tolerability profile of aclidinium was confirmed in the longer-term studies, LAS-MD-35 and the ACCORD COPD I extension (Table 1).34,35 In particular, major adverse cardiac events in pooled data were low, with no evidence of dose dependency (1.6% events with aclidinium 200 µg BID and 1.4% events with aclidinium 400 µg BID).40 In the 6-week study comparing aclidinium with placebo and tiotropium, the incidence of AEs (28.0% overall) was similar between treatment groups, with few patients experiencing anticholinergic AEs (<2.0%, any group).36 Further confirmation of the tolerability of aclidinium is provided by the Cochrane meta-analysis, including ten trials and 5,651 patients, which found no significant difference in the occurrence of AEs between aclidinium and placebo.40

Dose selection
Several of the Phase II and III studies described in this review included two doses of aclidinium – 200 µg and 400 µg BID; however, the data have not revealed a clear dose–response relationship. The 400 µg dose provides numerically greater improvements in most study endpoints compared with aclidinium 200 µg, although there are exceptions, such as the improvements in SGRQ observed over 64 weeks (Figure 4). However, these studies were not designed to directly compare the two doses, and confidence intervals often overlapped. As there are no apparent differences in the safety profile of the two doses, and the 400 µg dose consistently provided the greatest improvements, this was the dose licensed by the EMA and FDA.51,52

Discussion
As noted in the current GOLD guidelines, tiotropium, aclidinium, and glycopyrronium can all be considered as appropriate options for maintenance treatment in the stable COPD patient.2 This review concerned aclidinium in the context of two other LAMAs. What stands out as the difference between it and them, since they seem to have similar efficacy and safety profiles?

The low systemic bio-availability of aclidinium may be an advantage, but more data are needed, as this is a class of drugs with a generally low side-effect rate. The BID dosing does not appear to be a disadvantage compared to the QD regimes of tiotropium and glycopyrronium, since it may confer better overnight bronchodilation that may be particularly beneficial for patients with significant night and morning symptoms.

The three LAMAs also provide patients with a choice, as each is delivered by a different device, and some patients may prefer one over another. For example, the multidose Genuair®/Pressair® was preferred by more patients than the HandiHaler®.44 More importantly, the critical error rate (errors of use that potentially result in poor lung deposition of the drug) was lower with the aclidinium device than the HandiHaler®. The device plays a crucially important role in determining the reliability of inhaled therapy, since poor technique is associated with increased health care resource use.53

In conclusion, when considering new inhaled drugs, it is important to look beyond the chemical entity and its pharmacology. Dosing regimens and inhaler performance may be equally important in determining relative advantages of one drug over another. That may be the case with aclidinium.

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Disclosure
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